No evidence of benefit for universal screening with 75 g oral glucose tolerance test in polycystic ovary syndrome

Should the recently published PCOS guidelines be revised?

The recent supplement of the Journal titled "Assessment and management of polycystic ovary syndrome: summary of an evidence-based guideline" summarises the full Australian guideline document that was launched at the 2011 Endocrine Society of Australia Annual Scientific Meeting.[1] The document is thorough and has been put together meticulously; it covers the major diagnostic and management issues encountered by health professionals looking after patients with this challenging condition. However, the recommendations for metabolic screening included a 2-yearly 75 g oral glucose tolerance test (OGTT) in all women with polycystic ovary syndrome (PCOS), and annual testing for those with an additional risk factor.[1] I believe that this screening protocol is not based on evidence and should not be applied universally to women with PCOS.

Insulin resistance is a common feature in PCOS, and many studies have shown that even lean women with PCOS are insulin resistant compared with weight-matched controls.[2] However, although the major risk factors for abnormalities in glucose metabolism are amplified in these women, they are similar to those in the general population — namely age, obesity and family history of type 2 diabetes.[3] Given the young age of many patients with PCOS, and the fact that a significant minority (34% in one United States study[4]) have a normal body mass index (BMI), the diagnostic yield of 2-yearly OGTTs in some subgroups of women with PCOS is very low. The recommendation was taken directly from a position statement that was published by the Androgen Excess Society in 2007, in which it was acknowledged that some members of the expert panel disagreed with the recommendation and suggested a more targeted approach to screening.[5]

In a study of 372 Australian women with PCOS, only one of 73 women who had been diagnosed with diabetes had a BMI of less than 25 kg/m^2, but, in women in the cohort who were aged under 30 years (whose mean BMI was over 35 kg/m^2), the prevalence of diabetes was less than 2%.[3] Therefore 98% of women with PCOS under the age of 30 years could undergo an OGTT five times during their 20s with little chance of a clinical benefit. Should screening for impaired glucose tolerance, which is more common, be a sufficient reason to justify routine screening? In the same Australian study, the prevalence of impaired glucose tolerance in a very obese group was 13.4%.[3] A more recent report from the US showed that only 3% of non-diabetic women with PCOS and a BMI of less than 25 kg/m^2 had impaired glucose tolerance.[6] Furthermore, among the principles of screening are (i) that there must be evidence that diagnosing the condition being screened for leads to treatment which is better at an earlier stage and (ii) that there should be an agreed policy on who to treat.[7] Such evidence does not exist for impaired glucose tolerance screening in PCOS.

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Possible predictors of progression from normal glucose tolerance to abnormal glucose metabolism in PCOS have been examined. In a Canadian cohort of patients with PCOS, the best predictor of later abnormal glucose tolerance was a glucose excursion of more than 1.4 mmol/L in the initial OGTT (ie, that which returned a normal result).[8] Confining future screening to those women who fulfilled this criterion would reduce the number of the OGTTs performed by 45%.[8] Decision tree modelling is another technique that has been used to enable targeted screening of women with PCOS.[9] Even a decision tree which uses clinical data alone (ie, age, BMI, waist circumference and waist-to-hip ratio) would reduce the number of OGTTs performed by 25%, without missing a single case of impaired glucose metabolism.[9]

While intuitively it would seem that delaying or preventing the diagnosis of diabetes would be good, in practice this just means a change in the glucose threshold at which intervention commences. Considering that recent large studies of type 2 diabetes have shown no evidence that aggressive glucose lowering improves macrovascular outcomes, and that it may increase mortality,[10,11] we are far from a situation where earlier glucose lowering intervention in "prediabetes" is of proven benefit. The mainstay of treating patients with impaired glucose tolerance is lifestyle change and, in some cases, metformin therapy[12] — established therapies for PCOS that are covered later in the guideline document.[1] Some experts have stated that metformin should only be used to treat PCOS in the settings of diabetes and impaired glucose tolerance (and possibly in adolescence) and should not be used to manage infertility or hirsutism.[13] This is a narrower opinion than expressed in the Australian guideline and ignores the beneficial effects that metformin may have in inducing ovulation in women with a BMI of less than 30 kg/m^2 or when combined with clomiphene citrate.[1] Diagnosing impaired glucose tolerance in PCOS may not lead to any particular change in management, with lifestyle change and/or metformin still the mainstay. The exception to this is women seeking to become pregnant, in whom early recognition of an abnormality in glucose metabolism enables earlier treatment and improved fetal and maternal outcomes. Predominantly though, the main

diagnosis of importance from an intervention viewpoint is type 2 diabetes.

My concern is that practitioners who choose to perform selective OGTT screening in patients with PCOS (based on age, BMI, waist circumference, family history of diabetes and a wish to become pregnant) will be seen as "not following the guidelines". Patients do not find the OGTT a pleasant experience. Non-selective, frequent repetition of the OGTT in women with PCOS will create an unnecessary burden for many patients, with no proven benefit. Larger prospective studies are needed to examine whether the intensive screening protocols recommended in the Australian guideline and the intervention which arises from an abnormal result are superior to universal lifestyle advice and selective screening of women with PCOS who have a substantially increased risk of diabetes.

I urge the authors of this otherwise excellent document to revise their recommendations to state that performing a 2-yearly OGTT in *all* women with PCOS has an extremely low yield of abnormality in certain subgroups and that no evidence of benefit exists in diagnosing impaired glucose tolerance over and above the usual treatment recommended for this common condition. Until such evidence is available, a more targeted approach to screening for glucose metabolism abnormalities in PCOS should be suggested.

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